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Maximizing positive outcomes for patients with staphylococcal infections

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Abstract

Maximizing positive outcomes for serious Gram-positive infections, such as those caused by *Staphylococcus* species, requires an aggressive treatment approach. Although specific approaches will depend upon many factors, the underlying common strategy should recognize the positive contribution of minimizing complications and inpatient treatment duration and the efficient use of healthcare resources, while also focusing on rapid resolution of infection and safety and tolerability. To advance the standard of care for patients, we need to utilize therapies that enable such a range of factors to be improved. Treatment guidelines are useful to establish evidence-based standards of care, but they are updated infrequently and there is currently no pan-European consensus for the treatment of staphylococcal infections. With the benefit of the clinical experience that has been acquired for the most recently licensed antibiotics, together with an appreciation of the appropriate usage of older agents, there are good prospects for achieving positive outcomes earlier and in a greater range of patients with staphylococcal infections, and treatment guidelines should be updated regularly to reflect this.

Keywords: Bloodstream infections, daptomycin, Gram-positive infections, infective endocarditis, *Staphylococcus aureus*

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Introduction

Despite recent advances, Gram-positive infections remain a significant cause of morbidity and mortality among hospitalized patients and are the cause of various serious hospital-acquired and community-acquired infections [1]. In order to maximize positive outcomes for patients, aggressive treatment approaches against the opportunistic pathogens that are the major causative agents of these infections are required. Of particular note for its pathogenicity is *Staphylococcus aureus*, methicillin-resistant strains of which have become more prevalent in some countries and are associated with greater morbidity and mortality than wild-type strains [2].

The past decade has witnessed significant changes in the profiles of susceptibility of Gram-positive bacteria to vancomycin, a traditional treatment of choice for serious infections caused by methicillin-resistant *S. aureus* (MRSA). These include the emergence of vancomycin-resistant staphylococci and enterococci, as well as vancomycin-intermediate *S. aureus* and heteroresistant vancomycin-intermediate *S. aureus* [3,4]. Furthermore, several reports indicate that the MICs of vancomycin for susceptible strains have increased over time in some healthcare institutions [5–8], and that this has had a negative impact on the clinical outcomes for patients [9–11]. This changing epidemiology serves to emphasize the difficulty of ensuring that patients receive appropriate antibiotic therapy.

Specific treatment approaches to staphylococcal infections will depend upon many factors, including the species, strain and site of infection, as well as the presence of any co-morbid conditions. However, the underlying common strategy should recognize universal goals of treatment that include minimizing the risk of complications experienced during prolonged infection, minimizing time spent in hospital and optimizing the use of limited healthcare resources. Therefore, the ideal antibiotic will resolve infection rapidly and completely, and will have a good safety and tolerability profile and a convenient dosing regimen. Each of these key features will be discussed in further depth in this review.

Minimizing Complications in Staphylococcal Infections

If not treated effectively and rapidly, patients with Gram-positive infections are at risk of developing serious complications. In a recent surveillance programme in Scotland, hospital-acquired infections contributed to mortality in 13% of all deaths [12]. Surgical site infections (SSIs) are some of the most frequent nosocomial Gram-positive infections, with incidence rates of up to 18%, even after clean surgery [13]. *S. aureus* continues to be a major cause of SSIs, being responsible for nearly 45% of orthopaedic-related SSIs in the UK between 2004 and 2007, with 62% of these being caused by MRSA [14]. A review of 3254 deaths of patients in all specialties of surgical care in Scotland during 2006 found that in 7% of the deaths that followed surgery, infection had developed at the operation site, and that 4% of all patients had hospital-acquired MRSA at the time of death [12]. Therefore, it would appear that effective management of these infections continues to be a significant challenge.

New antibiotics are continuously being developed, particularly for staphylococcal infections resistant to semi-synthetic penicillins. In light of the increasing number of available antibiotic agents, continuous reappraisal of treatment options is necessary to ensure that patients benefit maximally from these pharmaceutical advances; antibiotic agents with alternative modes of action may warrant particular consideration. Daptomycin (Cubicin) is the first available agent from a new class of antibiotics, the cyclic lipopeptides. The efficacy of daptomycin for patients with complicated skin and soft tissue infections (cSSTIs) was compared with that of conventionally recommended antibiotics (penicillinase-resistant penicillins or vancomycin) [15]. Response rates were similar among treatment groups, across all baseline diagnoses, with overall success rates of 83.4% and 84.2% for the daptomycin and comparator groups, respectively [15].

Bloodstream infections (BSIs) constitute a potential complication of many peripheral infections, including SSIs, and represent a route by which these can give rise to numerous serious complications, which may be localized, such as infective endocarditis (IE), infections of bones, joints or implanted devices, myositis, epidural abscess or meningitis, or systemic, such as systemic inflammatory response syndrome [16,17]. For patients with BSIs, MRSA and time to culture positivity (a surrogate marker for the size of the inoculum) have been reported as independent predictors of death [18]. Thus, BSIs are justifiably considered to be a medical emergency, especially when *S. aureus* is the suspected pathogen.

For many years, semi-synthetic penicillins and vancomycin have been the pillars of treatment for *S. aureus* BSIs. For methicillin-sensitive *S. aureus* (MSSA), the greater efficacy of β-lactams relative to vancomycin is well documented, despite the susceptibility of MSSA to vancomycin *in vitro* [19–22]. For example, in a multicentre, prospective observational study of 505 consecutive patients with *S. aureus* bacteraemia (SAB), nafcillin proved superior to vancomycin for the treatment of MSSA. Furthermore, therapy with vancomycin was significantly associated with relapse of infection [19]. One of the key strengths of vancomycin has been in the treatment of MRSA infections, although data now support a more sophisticated approach to its choice than reliance on a positive susceptibility test. Recent reports suggest that the efficacy of vancomycin against MRSA strains with a vancomycin MIC of ≥1.5 mg/L may be compromised [11,23]. Therefore, although vancomycin remains an effective treatment for many Gram-positive infections, clinicians may need to consider alternatives when the methicillin status of a suspected *S. aureus* infection is uncertain or when susceptible MRSA strains with vancomycin MICs at the upper end of the susceptible range have been identified or are suspected on the basis of local epidemiology. Daptomycin, as an alternative to these standard therapies, has demonstrated efficacy in complicated and uncomplicated SABs as well as right-sided IE in a recent study, despite there being few relevant patients for this specific indication (Fig. 1) [24]. In this study, daptomycin was proven to be effective against both MSSA and MRSA, and as such, may theoretically be advantageous over currently licensed agents for the empirical treatment of Gram-positive infections.

Rapid Resolution of Infection

In order to maximize patient benefit, the optimal treatment regimen should ensure the prompt administration of an appropriate antibiotic agent. However, a survey of physicians

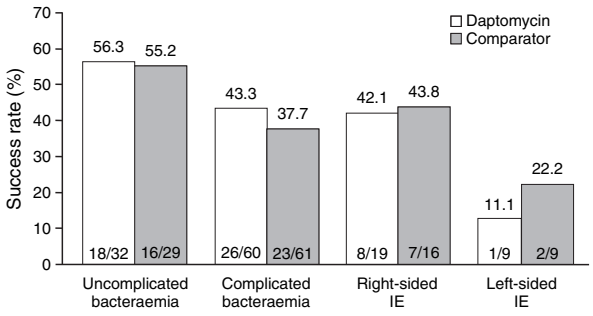

FIG. 1. Daptomycin success against *Staphylococcus aureus* bacteraemia and infective endocarditis (IE) in a phase III trial [24].

(*n* = 605) from the European G5 countries (France, Germany, the UK, Italy and Spain) revealed that *c.* 50% of patients with MRSA receive inappropriate first-line therapy [25]. Patients receiving delayed or inappropriate therapy are at increased risk of mortality [26,27]. Lodise *et al.* [26] found that delayed treatment was an independent predictor of infection-related mortality (OR 3.8; 95% CI 1.3–11.0; p =0.01) and was associated with a longer hospital stay than early treatment (20.2 days vs. 14.3 days; p =0.05) for patients with hospital-acquired SAB. Similarly, in a different study, a statistically significant relationship was found between the rates of inadequate antimicrobial therapy and associated mortality, with reported mortality rates of 62% vs. 28% for patients receiving inadequate vs. adequate therapy, respectively (p <0.001) [27]. Ideally, in addition to its prompt administration, an appropriate antibiotic agent should have a rapid onset of action and reliably deliver therapeutic serum concentrations after administration of the first dose. Therefore, appraisal of the antibiotic options for any patient should include consideration of their pharmacokinetic and pharmacodynamic profiles.

Optimal dosing of glycopeptides is achieved by therapeutic drug monitoring and/or loading doses. The typical dose of vancomycin (1 g every 12 h, intravenously) achieves trough serum concentrations of 5–10 mg/L [28,29]; however, a study in patients with bacteraemia concluded that patients were more likely to become afebrile within 72 h if vancomycin trough concentrations were ≥10 mg/L [30]. It is typically recommended that vancomycin dosing is adjusted to achieve trough levels of 10–15 mg/L. Achieving therapeutic serum concentrations with teicoplanin may also require dosing adjustments. Pharmacokinetic analysis has predicted that therapeutic trough levels of ≥10 mg/L are achieved after 4 days of administration [31]. In clinical practice, steady state is achieved slowly and requires in excess of 14 days of repeated administration for 93% of patients [32]. Therefore, loading doses (6 mg/kg every 12 h for at least three doses) are recommended as part of the standard dosing for patients with moderate and severe infections [31], and such doses are considered mandatory in all critically ill patients [33]. High loading doses may reduce the delay in attaining therapeutic concentrations; monitoring of teicoplanin serum concentrations might be helpful in certain patient groups to ensure that therapeutic concentrations are achieved [32]. In fact, the British Society for Antimicrobial Chemotherapy recommend therapeutic drug monitoring for patients with serious infections who are treated with teicoplanin [34].

Although there are different doses for the two indications of daptomycin, therapeutic drug monitoring is not required [35]. After multiple doses, plasma daptomycin concentrations remain consistent and predictable, with only small increases in peak plasma concentration and area under the plasma concentration–time curve values being noted from the first dose to the achievement of steady state (Fig. 2) [36]. With respect to pharmacodynamics, *in vitro* analysis of simulated endocardial vegetations has shown that daptomycin is rapidly bactericidal against both MSSA and MRSA after 24 h (decrease of 5.51 to 6.31 ± 0.10 $\log_{10}$ CFU/g), whereas neither vancomycin nor linezolid exhibited bactericidal activity throughout the 72-h experiment [37]. These results were corroborated in an *in vivo* animal model, in which daptomycin showed greater and more rapid bactericidal activity against MSSA than nafcillin or linezolid and against MRSA than vancomycin or linezolid (Fig. 3) [38]. In clinical trials, a rapid response was observed with daptomycin therapy in patients with cSSTIs. A greater proportion of daptomycin-treated patients than patients treated with conventional antibiotics achieved clinical success within the first 4–7 days of therapy (63% vs. 33%, respectively; p <0.001) [39].

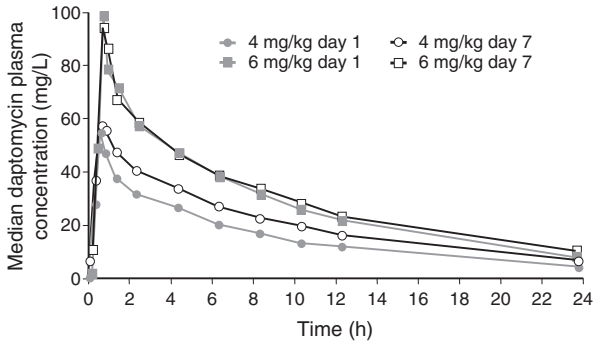

FIG. 2. Daptomycin plasma drug concentration over time for once-daily dosing of the 30-min intravenous infusion, adapted from reference [36], with permission from the American Society for Microbiology.

Pharmacokinetic–pharmacodynamic factors that may influence the rapidity of infection resolution may be tissue specific. For example, daptomycin interacts with and is inhibited by pulmonary surfactant, which renders it ineffective for simple bronchoalveolar pneumonia [40]. By contrast, the pharmacokinetic profile of linezolid makes it particularly suitable for the treatment of pneumonia. Linezolid has long plasma and intrapulmonary half-lives, and after a twice-daily 600-mg dose, the concentration of linezolid in both plasma and pulmonary epithelial lining fluid exceeds the susceptibility breakpoint for Gram-positive bacteria [41,42].

Minimizing Inpatient Treatment Duration

It is generally recognized that returning the patient to the community at the earliest possible time is not only beneficial

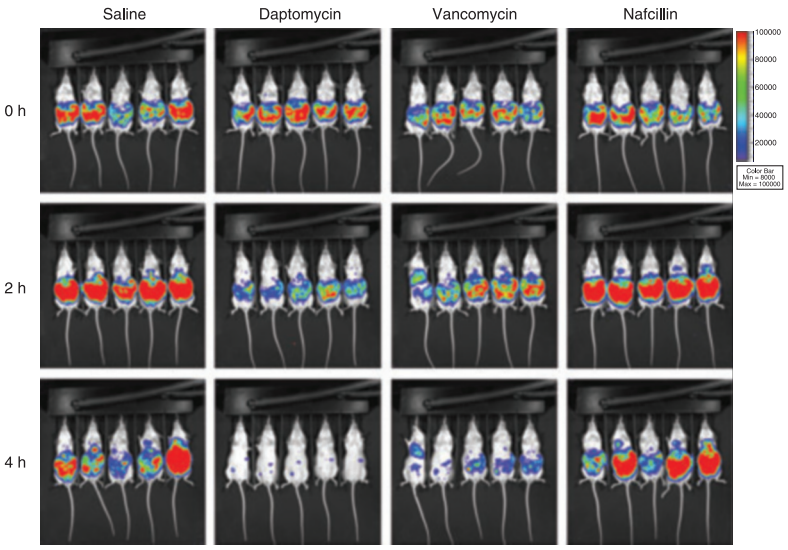

FIG. 3. *In vivo* activity of daptomycin, vancomycin and nafcillin against methicillin-resistant *Staphylococcus aureus* (MRSA) peritonitis in healthy rats. Luminescent images of MRSA (Xen-1) peritonitis in healthy rats. Groups of mice (n = 5/group) were anaesthetized with isoflurane and imaged for 3 min at 0, 2 and 4 h after being dosed with 10 mL/kg saline, 50 mg/kg daptomycin, 100 mg/kg vancomycin or 100 mg/kg nafcillin. Reproduced from reference [38], with permission from the American Society for Microbiology.

for the patient, but will also reduce the pressure on limited hospital resources. With the total annual cost of treating nosocomial MRSA BSIs in Europe estimated at €117 million (Verhoef *et al.* http://www.scoreproject.org/SCORE_met_ISBN.pdf), health economics is an increasingly important component of healthcare protocols. Direct drug costs contribute only a fraction of the overall treatment costs. Treatment with antimicrobials that have extended infusion periods, require therapeutic drug monitoring or have a slow onset of action may serve to prolong the duration of hospitalization for the patient, thereby impacting on the total costs of treatment [43]. Moreover, a longer hospital stay increases the risks of both nosocomial infection and transmission of infection to other hospitalized patients [44].

Evaluation of economic outcomes has indicated that daptomycin is more cost-effective than vancomycin in the treatment of cSSTIs [39]. As compared with patients treated with vancomycin, daptomycin-treated patients achieved a more rapid resolution of symptoms within 3 days (90% vs. 70%; $p < 0.01$), and a greater proportion experienced clinical improvement (98% vs. 81%; $p < 0.01$) within 5 days. Treatment with daptomycin was also associated with a shorter duration of intravenous therapy (median, 4 days vs. 7 days; $p < 0.001$) and antibiotic-related hospitalization (median, 4 days vs. 8 days; $p < 0.001$) than treatment with vancomycin. The total cost of hospitalization was significantly reduced in the daptomycin-treated group as compared with the vancomycin-treated group (median, US$ 5027 vs. US$ 7552; $p < 0.01$).

One obvious way to reduce the duration of hospital stays is for antimicrobial therapy to be administered in an outpatient setting, and agents with oral administration may be particularly advantageous for some patients. Linezolid is available as both intravenously and orally administered formulations. The oral formulation of linezolid maintains 100% bioavailability, which means that patients can be switched from inpatient to outpatient therapy without the need for dosage adjustment [45,46]. Clinical studies suggest that outpatient treatment with oral linezolid is both efficacious and cost-effective [47,48].

Notwithstanding the benefits of orally administered antimicrobial agents, outpatient parenteral antimicrobial therapy (OPAT) is increasingly an option for patients with non-serious infections who are medically stable and whose infections are responding to treatment. Parenteral administration rapidly achieves peak serum concentrations, and administration by a healthcare professional, either in the community or in an outpatient setting, might facilitate compliance, thereby potentially reducing the risk of the emergence of resistant strains. The potential for relapse of infection or for the spread of infection to the community are also reduced if compliance is ensured. Key attributes of antimicrobial agents considered for OPAT include proven efficacy and a good safety and tolerability profile, as well as a long half-life, so that they require infrequent administration. Antimicrobial agents with a short administration time and no requirement for therapeutic dose monitoring may also be advantageous for use in an ambulatory setting.

Teicoplanin may be particularly suitable for outpatient administration, owing to its once-daily intramuscular injection, and as such has been one of the most frequently selected antibiotic agents for European OPAT programmes [49,50]. Experience of OPAT with daptomycin is increasing, and the evidence to date suggests that it is both safe and effective for use as OPAT in patients with Gram-positive infections. Analysis of data from the Cubicin Outcomes Registry and Experience (CORE)—a US retrospective post-marketing database of daptomycin-treated patients—showed a

higher rate of clinical success for OPAT patients than for those receiving daptomycin on an inpatient basis (94.6% vs. 86.3%, respectively; p <0.001). However, this difference may be attributable to differences in the baseline characteristics of the two groups, as OPAT patients were younger and had fewer underlying diseases than inpatients. There was no significant difference in the occurrence of daptomycin-related adverse events between the two groups (5.8% and 8.3% for the OPAT and inpatient groups, respectively; p =0.12) [51].

A recent analysis has suggested that daptomycin might be an appropriate treatment option for patients with SAB/IE completing their therapy in the outpatient setting. Outcomes for patients treated as part of a randomized trial that compared daptomycin with standard therapy (semi-synthetic penicillin or vancomycin, each with 4 days of concomitant low-dose gentamicin) [24] were assessed according to treatment setting. Patients who received a portion of their antimicrobial treatment outside of the hospital had a higher rate of clinical success at the test-of-cure visit than those who completed their full course of therapy as inpatients (86.4% vs. 55.7%; p <0.001). Within the OPAT group, clinical success rates were reported to be similar for patients treated with daptomycin and those treated with standard therapy (90% and 83%, respectively). Persistent infection and relapse were less frequent in the OPAT group than in the inpatient group, and OPAT was associated with fewer deaths than inpatient treatment (3.9% vs. 18.6%; p =0.001) [52].

A randomized phase I study assessed the safety and tolerability of daptomycin administered as a 2-min intravenous injection [53]. The daptomycin 2-min intravenous injection was well tolerated, with no serious or severe adverse events after administration of either a single dose or once-daily injections of both 4 and 6 mg/kg for a period of seven consecutive days. No clinically significant differences in pharmacokinetic parameters were observed when daptomycin was administered as a single 2-min intravenous injection as opposed to the standard 30-min intravenous infusion. The daptomycin 2-min intravenous injection has been submitted for regulatory review, and the results of this study suggest that it might be particularly suitable for use in the outpatient setting.

Maximizing Safety and Tolerability

For any given treatment regimen, the safety and tolerability of administered agents are of paramount importance. This is brought more sharply into focus with critically ill patients, such as those in an intensive-care unit, who may have co-morbid conditions, or for patients with renal insufficiency. Aside from their potential for inducing hypersensitivity reactions, β-lactams are generally regarded as some of the best-tolerated antibiotics. Vancomycin is dose-limited by the risk of nephrotoxicity, which can be managed by therapeutic dose monitoring and dose reductions for patients with renal impairment. The safety and tolerability of daptomycin have been compared with these standards of care (initial low-dose gentamicin in combination with either an anti-staphylococcal penicillin or vancomycin) in two phase III studies in patients with cSSTIs [15] as well as in patients with SAB/IE [24]. In all three studies, the overall incidence of adverse events after treatment with daptomycin or comparator antibiotics was found to be similar. Furthermore, the majority of adverse events after daptomycin treatment were judged to be unrelated to the study treatment and were of mild to moderate severity. Although increases in plasma creatine phosphokinase (CPK) were noted in daptomycin phase I studies [35], close monitoring of CPK in the cSSTI study, which included more than 1000 patients, revealed no clinically or statistically significant differences in the distribution of CPK values at baseline or throughout the study duration [15]. In the SAB/IE study, creatinine kinase elevations were significantly more frequently observed in the daptomycin group than in the standard therapy group (6.7% vs. 0.9%, respectively; p =0.04). Significantly fewer daptomycin-treated patients experienced renal impairment than those in the comparator group (6.7% vs. 18.1%, respectively; p =0.009) [24]. In the USA, no dose adjustments are required when prescribing daptomycin for patients with mild to moderate renal impairment [54]. In Europe, dose adjustments are not required for patients with mild to moderate renal impairment (creatinine clearance (CrCl) ≥30 mL/min) who are being treated for cSSTIs without SAB [35]. No recommendations have been made regarding dose reductions of daptomycin for patients with right-sided IE or cSSTIs associated with SAB, and its use in these indications for patients with CrCl <50 mL/min must be justified by clinical benefit outweighing the potential risk. For cSSTI patients with severe renal impairment (CrCl <30 mL/min), it is recommended that the dosing frequency of daptomycin be extended to every 48 h.

Implementation of Therapeutic Advances

Treatment guidelines are important for the establishment of evidence-based standards of care. However, many guidelines are updated infrequently and are often focused on prophylaxis or may be diagnosis-specific. Moreover, many are country-specific, and there is currently no pan-European consensus for the treatment of staphylococcal infections. In light of the changing epidemiology and the continued introduction of newer antimi-

crobial agents, regular reviews of treatment guidelines become of increasing importance. A recent publication has provided the rationale for the inclusion of daptomycin in guidelines for the treatment of bacterial IE caused by staphylococci. It is of note that the importance of bactericidal activity for effective treatment of IE is recognized [55].

Summary and Conclusions

Prompt treatment that provides appropriate empirical coverage with rapidly acting bactericidal agents that promptly and reliably reach therapeutic concentrations will assist in achieving rapid recovery from infection with minimal complications, while ensuring the cost-effectiveness of healthcare provision. Newer antibiotics might have both the potency required for the effective treatment of staphylococcal infections with reduced susceptibility to the current standard of care and the option of outpatient administration. Clear, evidence-based treatment guidelines, up to date with regard to licensed agents and epidemiological developments, will facilitate the implementation of treatment protocols that have the potential to maximize outcomes for patients with staphylococcal infections.

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Transparency Declaration

J.-P. Stahl is a member of the Daptomycin International Advisory Board.

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